REMARKS

Claims 32-35 and 45-50 are pending and rejected. Claims 46-50 are withdrawn as not elected.

Applicants appreciate the Examiner's withdrawal of the rejections for Double Patenting and obviousness over Eversole.

CLAIM REJECTIONS UNDER 35 U.S.C. §112

Claims 32-35 and 45 are rejected under 35 U.S.C. 112 ¶1. The Examiner's position is that, while enabling for cyanine dyes of Formula 1, 2, 3, and 4, the claims are not enabling for all photodiagnostic and phototherapeutic dyes which may be administered to a subject.

Applicants disagree and assert that they have met the standards for enablement by communicating their invention to the public in a meaningful way, and that they have informed the public how to make and how to use their method.

The claims recite a method to enhance fluorescence of a dye. Thus, the dye must be a one that is known to be fluorescent. The public would know, by performing the claimed method, whether or not the fluorescence of the dye is enhanced.

As addressed in the attached Declaration under 37 C.F.R. §1.132, a person of ordinary skill in the art knows which dyes are fluorescent, knows how to determine whether or not a prospective dye is indeed fluorescent, knows how to monitor fluorescence, and knows how to determine if fluorescence is enhanced by performing the method. Thus, the public is informed how to make and how to use the claimed method.

Claims 32-35 and 45 are rejected under 35 U.S.C. 112 ¶2 as indefinite because the Examiner asserts that it is unclear what other dyes other than cyanine dyes of Formulas 1, 2, 3, and 4 are disclosed.

Applicants respectfully disagree. As analyzed in the attached Declaration under 37 C.F.R. §1.132, dyes other than cyanine dyes of Formulas 1, 2, 3, and 4 include those dyes that are known to be fluorescent. The method recites that it is one for enhancing fluorescence, which requires at least a threshold level of fluorescence of the dye. The method recites that the dyes be administrable to a patient for a photodiagnostic or phototherapeutic procedure, which requires a dye that is used in a photodiagnostic or phototherapeutic procedure.

For at least these reasons, Applicants assert that the claims are enabled and definite, and respectfully requests the rejection be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. §103

Claims 32-35 and 45 are rejected under 35 U.S.C. §103(a) as obvious over Licha U.S. Patent No. 6,083,485 in view of Song.

Applicants have amended claim 32 to require that the solvent is added to the dye prior to the resulting composition being administered to a patient.

With this Amendment, Applicants submit a Declaration under C.F.R. §1.132. The Declaration resubmits arguments filed by Applicants' representative in the March 3, 2008 Amendment as arguments now from the Declarant, and also addresses the July 24, 2008 obviousness rejections by analyzing why a person of ordinary skill in the art would not find that Licha in view of Song renders Applicants' method obvious.

Applicants respectfully assert for at least the above reasons, the rejection is overcome and requests its withdrawal.

CONCLUSION

Applicants believe the application is in complete condition for allowance. No fees are believed due but, if deemed necessary, the Office is authorized to charge them to Deposit Account No. 20-0809.

Respectfully submitted,

THOMPSON HINE LLP

/Beverly A. Lyman/

Beverly A. Lyman, Ph.D.
Reg. No. 41,961

Intellectual Property Group
P.O. Box 8801
Dayton OH 45401-8801
Direct Dial 513 352 6596

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Serial No.	10/800,531
Filing Date	March 15, 2004
Confirmation No	2309
Applicants	Achilefu et al.
Title	**RECEPTOR AVID EXOGENOUS OPTICAL AND THERAPEUTIC AGENTS**
Group Art Unit:	1618
Examiner	Jones, Dameron Levest
Attorney Docket No.	1448.2 H US (073979.40)

Cincinnati OH 45202 October 13, 2008

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22311450

DECLARATION OF WILLIAM L. NEUMANN, Ph.D.
PURSUANT TO 37 C.F.R. §1.132

I, William L. Neumann, declare as follows:

I am a former employee of Mallinckrodt Inc., the Assignee of the above-identified patent application. I am currently Assistant Professor in the Department of Pharmaceutical Sciences at Southern Illinois University Edwardsville. My Curriculum Vitae is attached.

I hold a Ph.D. in organic chemistry from the University of Missouri St. Louis. I have over 20 years of experience in the preparation and use of compounds for medical diagnosis and therapy, which is the subject of the application. I have read the January 4, 2008 and July 24, 2008 Office Actions and understand the position of the Examiner.

The Examiner rejects claims 32-35 and 45 as not enabled for all photodiagnostic and phototherapeutic dyes which may be administered to a subject other than cyanine dyes of Formulas 1, 2, 3, and 4.

I respectfully disagree. The claims recite a method to enhance fluorescence of a dye that is administered to a patient in a photodiagnosis or phototherapeutic procedure. A person of

ordinary skill in the art knows the identity of such dyes, or can readily determine their identity without undue experimentation.

For example, the dye must be one that is known or readily discernable to be fluorescent and administrable to a patient for photodiagnosis or phototherapy. For example, Licha U.S. Patent No. 6,083,485, of record, discloses examples of such dyes:

> Examples of using dyes for in-vivo diagnostics in humans are photometric methods of tracing in the blood to determine distribution areas, blood flow, or metabolic and excretory functions, and to visualize transparent structure of the eye (ophthalmology). Preferred dyes for such applications are indocyanine green and fluorescein [citations omitted] (col. 1 line 66 to col. 2 line 5, emphasis added)
>
> ...
>
> Photosensitizers designed for use in photodynamic therapy (PDT) (including haematoporphyrin derivatives, photophrin II, benzoporphyrins, tetraphenyl porphyrins, chlorines, phthalocyanines) were used up to now for localizing and visualizing tumours [citations omitted] (col. 2 lines 17-20, emphasis added).
>
> ...
>
> ...for detecting breast cancer and ... the known fluorescein, fluorescamin, and riboflavin as contrast-improving absorption dyes (col. 2 lines 29-33, emphasis added)
>
> ...
>
> ...an in-vivo method for the fluorescence detection of tumours using the following photosensitizers: haematoporphyrin and its derivative (Hp and HpI), uro- and copro- and protoporphyrin as well as numerous mesosubstiituted porphyrins, and dyes such as riboflavin, fluorescein, acridine orange, beberine sulfate and tetracyclines (col. 2 lines 54-59, emphasis added).
>
> ...
>
> ...an in-vivo diagnostic method based on near infrared radiation (NIR radiation) that uses water-soluble dyes and their biomolecule adducts, each having specific photophysical and pharmaco-chemical properties, as a contrast medium for fluroescence and transillumination diagnostics in the NIR range, to new dyes and pharmaceuticals contains such dyes (Abstract, general Formulas I, I, and III at col. 4 lines 35 to col. 8 line 30, emphasis added).

Such examples are representative only and not exclusive.

A person of ordinary skill in the art knows how to monitor fluorescence of such a dye. For example, Licha U.S. Patent No. 6,083,485, of record, discloses examples of such fluorescence monitoring methods:

> Fluorescent images can be recorded using various methods. Preferred are those methods where the tissue is irradiated

> extensively, fluorescence information is visualized in local resolution by a CCD camera, or where the tissue sectors to be imaged are scanned by a light ray concentrated in a fibre optical waveguide and signals obtained are converted into an image by computing. The light is beamed in the narrow-band range at wavelengths close to the maximum absorption or at fluorescence-exciting wavelengths of the compounds of the invention. (col. 8 lines 50-60, emphasis added)

Such examples are representative only and not limiting.

A person of ordinary skill in the art knows how to determine if fluorescence is enhanced by the claimed method. For example, a person of ordinary skill in the art can perform comparison studies and can determine differences in fluorescence in the absence of the method and in the presence of the method.

I therefore respectfully assert that the claims are sufficiently enabled.

The Examiner rejects claims 32-35 and 45 as indefinite because it is unclear what other dyes other than cyanine dyes of Formula 1, 2, 3, and 4 are disclosed.

I respectfully disagree. A person of ordinary skill in the art knows, or can readily determine without undue experimentation, the dyes used in medical imaging (photodiagnosis and phototherapy) that are known to be fluorescent. The method recites that it is one for enhancing fluorescence, which requires at least a threshold level of fluorescence of the dye. The method recites that the dyes be administrable to a patient for a photodiagnostic or phototherapeutic procedure, which requires a dye that is used in a photodiagnostic or phototherapeutic procedure. I have previously listed examples of such dyes that Licha has disclosed.

I therefore respectfully assert that the claims are sufficiently definite.

The Examiner rejected (January 4, 2008 Office Action) claims 32-35 as obvious over Licha U.S. Patent No. 6,083,485. The Examiner cites Licha as disclosing that its dyes may be added to an-octanol/Tris buffer (column 9 lines 54-64). The Examiner rejects Applicants' claims as obvious because

> while Licha et al do not specifically state that fluorescence is enhanced when the dye is in the presence of the compatible organic solvent, a skilled practitioner in the art would recognize that since both Applicant and Licha et al disclose dyes in combination with a biocompatible organic solvent (i.e., isopropanol), it would be inherent that in both instances fluorescence. [*sic*]

The Examiner also states that because Applicants and Licha disclose the same components, and because a composition is inseparable from its properties, enhanced fluorescence would be exhibited by Licha's composition.
I respectfully disagree with the Examiner's position.

Licha does not disclose adding an organic solvent to a dye that is administered to a patient. In contrast, Licha adds an organic solvent pre-administration to a patient, to determine dye equilibrium properties. This does not teach, suggest, or motivate the claimed use of a dye added to a solvent in the claimed concentration to result in a composition that is administered to a patient to enhance dye fluorescence. Thus, a person of ordinary skill in the art would not look to Licha because Applicants' fluorescence enhancement is not required for Licha's process of equilibrium partitioning.

I respectfully assert that a person of ordinary skill in the art knows that adding n-octanol/Tris buffer to any agent is a well known method to provide a hypothetical equilibrium measurement of the agent between n-octanol/water (or aqueous buffer), or membrane/water phases.

In support of my assertion, my Representative submitted three references with March 3, 2008 Amendment, namely:

> Barton et al. J. Pharmaceutical Sciences (1997) 86, 1034
>
> Leo et al. "Partition coefficients and their uses". *Chem Rev* 71 (1971), 6, 525 (see at least the paragraph spanning pp. 525-526, the paragraph at the bottom of col. 1 p. 527, spanning p. 540-541, and the paragraph at the bottom of col. 2 p. 541)
>
> Moriguchi et al. (1992) "Simple method of calculating octanol/water partition coefficient" *Chem Pharm Bull* 40, 1, 127

These are exemplary only, and I respectfully request permission to supplement this list should the Examiner request more references from each group.

The Examiner cites Licha examples 2 and 7 as disclosing a dye dissolved in isopropanol. I respectfully disagree that these examples render the claimed method obvious because, in each, isopropanol is used in a "purification/isolation" procedure to purify or isolate the compound, as known by a person of ordinary skill in the art. In such purifications or isolations, isopropanol is removed and the crystalline purified compound is recovered. Hence, I respectfully assert that Licha does not teach, motivate, or suggest a compound's inherent fluorescence properties, if any, are enhanced by the organic solvent. In fact, Licha does not teach an organic solvent present along with the dye that is to be administered, as amended claim 32 recites.

The Examiner states

> ...since a composition is inseparable from its properties, if both Applicant and the cited prior art disclose adding a dye to a biocompatible organic solvent, then the properties will be similar regardless of whether the biocompatible organic solvent is added later.

Assuming *arguendo* the validity of the Examiner's statement, which I do not concede, a person of ordinary skill in the art would not simply add a dye during a photodiagnostic or phototherapeutic procedure, as opposed to adding a dye during the making of the composition, at least because there is undesirably less control over a composition that results from separate injections of each of two components, than from a single injection of a pre-formulated composition.

The Examiner cites Licha for disclosing "the composition may be administered intravenously" (col. lines 43-44) and "that the dyes should meet the requirements that generally apply to diagnostic pharmaceuticals" (col. 3 lines 35-55). These statements do not overcome the fact that Licha's solvents are used to determine dye equilibrium properties, the *in vitro* octanol/water distribution coefficient determination, and to precipitate the dye in an isolation and purification procedure.

Licha's composition does not render Applicant's imaging method obvious, because in Licha the administered composition does not contain an organic solvent. The Examiner also states that "...the skilled artisan would recognize that the crystal could be reconstituted if the composition is used for in vivo use, for example, in column 8, lines 31-37 and 42-44, it is disclosed that the composition may be administered intravenously." Licha, however, does not disclose the type of solvent that should be used to reconstitute dye crystals prior to administration but, as previously analylzed, Licha specifically states that the "dyes suitable for diagnostic purposes should be well soluble in water..." I assert that a person or ordinary skill in the art would be taught that Licha's solvent in the composition is water. Licha does not teach, suggest, or motivate adding to the composition any component to enhance the fluorescence of the dye.

Licha's use of an organic solvent is not for the claimed use and would not result in the claimed use. Licha's organic solvent, isopropanol, is to precipitate the compound in a purification procedure. It is not added to a dye and then administered to a patient. Licha does not teach DMSO to dissolve the dye or to prepare a dye in a DMSO/water solution.

The Examiner applies Song as teaching DMSO. However, Song does not overcome Licha's deficiencies, because Song teaches dissolving the dye in DMSO (p. 8232) *in vitro* to study Raleigh and hyper-Raleigh light scattering, not for *in vivo* imaging.

Thus, I respectfully assert that a person of ordinary skill would not combine Licha and Song, at least because Licha teaches use of an organic solvent, isopropanol, for purification of the compound to precipitate the dye in a purification step. Song teaches use of an organic solvent, DMSO, to dissolve the dye in an analytic step, namely, for spectroscopic analysis and comparison to other solvents. Neither Licha nor Song teach the combination of an organic solvent, such as DMSO for administration to a patient to enhance fluorescence of the dye in the imaging process.

For at least these reasons, I respectfully assert that a person of ordinary skill in the art would not find the claimed method obvious over Licha in view of Song.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

10-13-08

Date

William L. Neumann, Ph.D.

708279

Mailing Address:

212 W. Monroe
St. Louis, MO, 63122
H: (314) 984-8020, Cell: (314) 410-6282;
W: (618) 650-5166
wlneuman@siue.edu
wlneumann@att.net

Table of Contents

Research Interests:

Synthetic organic, bioorganic and medicinal chemistry, with major focus areas of structure based drug design, metal-mediated cross-coupling chemistry, biological chemistry of reactive oxygen and nitrogen species, and synthetic methods development for the total synthesis of biologically important molecules. Other interest areas include: The synthesis of chemical probes for the study of biological phenomena at the molecular, cellular and organism level; synthesis of functional multiphoton absorbing probes for cellular imaging and in vivo monitoring, the synthesis of conditionally activated smart molecules for biomedical and defense applications; metals and metal complexes in biological systems; new polymer and nanostructure-based actives delivery systems.

Industrial research includes leading drug discovery and development, including medicinal, organic, catalysis, bioorganic, nanoparticle and chemical and pharmaceutical process invention. Extensive experience directing scientific teams "from the lab." Medicinal chemistry experience includes the invention of novel antithrombotic leads, integrin antagonist leads, integrin-targeted chemotherapeutics, orally available synthetic enzyme mimetics, design and synthesis of functional fluorescent dye molecules, in addition to responding to FDA questions about drug chemistry and mechanism of action for Phase II clinical trials.

Mailing Address:

212 W. Monroe
St. Louis, MO, 63122
H: (314) 984-8020,
Cell: (314) 410-6282;

wneuman@siue.edu
wlneumann@att.net

Personal:

Date of Birth: December 16, 1958
Place of Birth: St. Louis, Missouri

Education:

B.S. in Chemistry, University of Missouri - Columbia, 1983
Ph.D. in Synthetic Organic Chemistry, University of Missouri – St. Louis, 1988, Advisor: Michael Sworin

Professional History:

2008 - present Assistant Professor of Pharmaceutical Sciences, School of Pharmacy, Southern Illinois University Edwardsville.

2005 – 2008 Principal Research Scientist – Biomedical Optics Discovery Research, Covidien-Mallinckrodt Inc., Hazelwood, MO.

- Chemistry Lead for the design and synthesis efforts for the discovery of new Near IR florescent dyes for application to intra-operative tissue mapping.
- Developed chemistry for the evaluation of structure-activity of a new class of optical probe molecules useful in real-time GFR-kidney function measurement. Invented molecule that is entering preclinical development.
- New approaches to phototherapy for oncology and surgical adhesion applications.

2006 – present Adjunct Professor – Department of Internal Medicine, Division of Pulmonary, Critical Care and Sleep Medicine.

2003-2005 - Associate Director of Discovery Chemistry, Metaphore Pharmaceuticals, St. Louis, MO.

- Directed a multi-disciplinary research team with the goal of developing a synthetic enzyme mimetic for human pharmaceutical use.
- Research included the design and synthesis of novel catalysts that function as powerful anti-oxidants for treatment of a variety of disease states which are associated with the over production of reactive oxygen and nitrogen species.
- Supervision of 4 Ph.D. and 2 BS/MS chemists.

2001-2003: Research Group Leader, Pharmacia-Pfizer, Discovery MedChem, Parallel Medicinal Chemistry Group, St. Louis, MO.

- Structure-based design and synthesis of selective Tissue-Factor-Factor-VIIa Inhibitors for use as novel antithrombotics.
- Research efforts included the design, validation and implementation of readily functionalized scaffold systems amenable to parallel medicinal chemistry SAR work using novel transitional metal-mediated cross-coupling methodologies.

- Large-scale validation of these methodologies as well as the synthesis of peripherals. Supervision of a group of 5-6 chemists.

1998-2001: Team Leader, Pharmacia Corp., Discovery MedChem-Chemistry and Process Technology Group, St. Louis, MO.

- New synthetic method development for bridging the gap between discovery and process.
- Design and synthesis of novel serine protease inhibitors for use as antithrombotics using novel cross-coupling chemistry.
- Design and synthesis of cancer cell specific integrin-targeted antitumor agents.
- Supervision of a group of 7-9 synthetic chemists on two medicinal chemistry projects.

1994-1998: Sr. Research Specialist, Monsanto Corporate Research, St. Louis, MO
1991-1994: Research Specialist, Monsanto Corporate Research, St. Louis, MO

- Design and synthesis of novel metal-based macrocyclic systems as functional mimics of the Superoxide Dismutase Enzymes.
- Extensive experience in the synthesis of chiral polyfunctionalized macrocyclic scaffolds.
- Bioconjugate chemistry applications of catalytic therapeutics and peptidomimetic targeting agents.
- Variable temperature NMR and IR studies of peptoid intramolecular hydrogen bonding motifs.
- Synthetic work on optimization of the aspartame process.
- Supervision of 2-3 synthetic chemists and NMR spectroscopist.

1989-1991 Sr. Research Chemist, Mallinckrodt Medical, St. Louis, MO.

- Design and synthesis of multidentate preorganized ligand systems for metal-based radiopharmaceutical applications.
- Incorporation of preorganized chelators into biologically active molecules.
- Development of synthetic methods: synthesis of air sensitive organophosphine compounds; synthesis of functionalized vicinal diamines.
- Supervision of 300 MHz NMR spectrometer (cryogenics and software maintenance).

1988-1989 Research Chemist, Mallinckrodt Diagnostics, St. Louis, MO.
1987-1988 Postdoctoral Fellow, Mallinckrodt Diagnostics, St. Louis, MO.

- Synthesis of tripodal encapsulating ligand systems for Tc-99m-based radiopharmaceutical development.
- Synthesis of radio-labeled Mitomycin derivatives.

Teaching:

1988-2000, Adjunct Professor of Chemistry, University of MO - St. Louis.

- Primarily responsible for teaching the evening college sections of the undergraduate organic chemistry series - Chemistry 261: Structural Organic Chemistry and Chemistry 262: Organic Reactions.

- Chemisty 306: Intermediate Organic Chemistry. Sections of Advance Organic Chemistry Courses and Special Topics courses.

1998-2000, Lecturer, Washington University, St. Louis, MO.

- Responsible for teaching the organic chemistry section of the MCAT review course.

Honors and Awards

- St. Louis Award (2007) St. Louis Section of the ACS

- Monsanto Reach Award (1996) for "Outstanding contributions to the Superoxide Dismutase Mimetic Program"

- Monsanto Reach Award (1994) for "Achievements relating to the Superoxide Dismutase Mimetic Program"

- Monsanto Achievement Award (1994) for the "Conception and Initiation of the Magnetic Resonance Imaging Program"

- Distinguished Alumni Lecturer, UM - St. Louis (1993) – Lecture: "The Asymmetric Synthesis of Functionalized Polyazamacrocycles"

- Monsanto Achievement Award (1992) for the "Development of the Cyclic Peptide Method for Polyazamacrocycle Synthesis"

- Mallinckrodt Presidents Award for Technical Innovation (1990) for "The Design and Synthesis of Unique Hexadentate Phosphine Ligand Systems for the Technetium - Heart Program" (Mallinckrodt Medical's Highest Science and Technology Prize).

- University of Missouri - St. Louis Alumni Fellowship (1987)
- Graduate School Fellowship (1985)
- Missouri Academy of Sciences Undergraduate Research Award (1982) – "Hydrogen-Deuterium Exchange Reactions of Ortho-Nitrotoluenes"

Professional Societies:

- American Chemical Society
- Division of Organic Chemistry
- Division of Medicinal Chemistry
- SPIE – Biomedical Optics
- Optical Society of America

Journal Review:

- Tetrahedron
- Tetrahedron Letters
- Organic Letters
- Journal of Organic Chemistry
- Organometallics

Departmental Service (Industrial):

- 2007 Early Development Advisory Board (Covidien)
- 2007 Searchable Compound Database Initiative (Covidien)
- 2006-2007 Corporate Chemical Hygiene Advisory Committee (Covidien)
- 2005-2006 NMR and LCMS Search Committee (Mallinckrodt)

- 2005-2007 Biomedical Optics Patent Disclosure Review Committee (Covidien)
- 2005-2007 LCMS and Preparative HPLC Service (Mallinckrodt-Covidien)
- 1999-2003 Lead "Walkup" Service for CPT group (Pharmacia-Pfizer)
- 1995 Actives-Delivery Representative (Monsanto Corporate)
- 1994 NMR Facility Committee (Monsanto Corporate)

Publications:

1. Nam S. Lee, William L. Neumann John N. Freskos, Tim A. Marzan, Jeng J. Shieh, Richard B. Dorshow, and Karen L. Wooley. Photonic Shell-Crosslinked Nanoparticle Probes for Optical Imaging and Monitoring. *Optical Society of America,* **2008** *(preprint).*

2. William Neumann, Richard B. Dorshow, Bethel Asmelash, Lori K. Chinen, Marin P Debreczeny, Richard M. Fitch, John N. Freskos, Karen P. Galen, Kimberly R. Gaston, Timothy A. Marzan, Amruta R. Poreddy, Raghavan Rajagopalan, and Jeng-Jong Shieh. Optical Probes For The Continuous Monitoring of Renal Function, *Proceedings of SPIE-The International Society for Optical Engineering* **2008**, *(Molecular Probes for Biomedical Applications II), in press.*

3. Trujillo, John I.; Huang, Horng-Chih; Neumann, William L.; Mahoney, Matthew W.; Long, Scott; Huang, Wei; Garland, Danny J.; Kusturin, Carrie; Abbas, Zaheer; South, Michael S.; Reitz, David B.: Design, synthesis, and biological evaluation of pyrazinones containing novel P1 needles as inhibitors of TF/VIIa. *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 4568-4574.

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8. Marmion, Mary E.; Woulfe, Steven R.; Neumann, W.L.; Nosco, Dennis L. Deutsch, Edward: Preparation and Characterization of Technetium Complexes with Schiff Base and Phosphine Coordination. 1. Complexes of Technetium-99g and -99m with substituted $acac_2en$ and trialkylphosphines (where $acac_2en$ = N,N'-ethylenebis[acetylacetoniminato]), *Nucl. Med. Biol.* **1999**, *26(7)*, 755.

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10. William L. Neumann, Gary Franklin, and Dennis Riley: Synthesis, Characterization, and Solution ^{113}Cd NMR Analysis of Cd(II) 1,4,7,10,13-Pentaazacyclopentadecane Complexes, *Coord. Chem. Rev.* **1998**, 174, 133 (*Invited Manuscript*).

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14. William L. Neumann, Gary W. Franklin, Kirby R. Sample, Karl W. Aston, Randy H. Weiss, and Dennis P. Riley: Synthesis of Conformationally Tailored Pentaazacyclopentadecanes. Preorganizating Peptide Cyclizations, *Tetrahedron Letters* **1997**, *38*, 779.

15. Dennis P. Riley, Susan L. Henke, Patrick J. Lennon, Randy H. Weiss, William L. Neumann, Willie J. Rivers, Jr., Karl W. Aston, Kirby R. Sample, Hayat Rahman, Chaur-Sun Ling, Jeng-Jong J. Shieh, Daryle H. Busch, and Witold Szulbinski: Synthesis, Characterization and Stability of Manganese(II) C-Substituted 1,4,7,10,13-Pentaazacyclopentadecane Complexes Exhibiting Superoxide Dismutase Activity, *Inorg. Chem.* **1996**, *35*, 5213.

16. Mary E. Marmion, Steven R. Woulfe, William L. Neumann, Gary Pilcher, Dennis Nosco: Synthesis and Characterization of Novel N_3O_3-Schiff Base Complexes of ^{99g}Tc, and *In Vivo* Imaging Studies with Analogous ^{99m}Tc Complexes, *Nuclear Med. And Biol.* **1996**, *23*, 567.

17. W.L. Neumann, R. Weiss, K. Sample, K. Aston, S. Henke, A. Modak, D. Riley: The Asymmetric Synthesis of Highly Functionalized Polyazamacrocycles via Reduction of Cyclic Peptide Precursors, *Tetrahedron Letters* **1994**, 35, 3687.

18. Mark A. Green, Carla J. Mathias, William L Neumann, Philip E. Fanwick, Michael Janik and Edward A. Deutsch: Potential Gallium-68 Tracers for Imaging the Heart with Positron Emission Tomography: Evaluation of Four Gallium Complexes with Functionalized Tripodal Tris(salicylaldimine) Ligands, *Journal of Nuclear Medicine* **1993**, *34*, 228.

19. William L, Neumann, Milorad M. Rogic, T. Jeffrey Dunn: The Stereoselective Synthesis of Functionalized Vicinal Diamine Systems by the Double Allylation Reactions of Protected 1,2-Bis-Imine Precursors, *Tetrahedron Letters* **1991**, *32*, 5865.

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21. W.L. Neumann, S. Woulfe, M. Rogic, J. Dunn: Versatile Methods for the Synthesis of Differentially Functionalized Pentaerythritol Amine Derivatives, *Journal of Organic Chemistry* **1990**, *55*, 6368.

22. M. Sworin, W. Neumann: Cyclopentanoid Synthesis via Directed Cationic Cyclization. Efficient Rearrangement of the Intermediate Cyclohexyl Cation, *Journal of Organic Chemistry* **1988**, *53*, 4894.

23. M. Sworin, W. Neumann: The Uncatalyzed Carbonyl Addition Reactions of 2-(1,3-Dioxolan-2-yl)ethylmagnesium bromide, *Tetrahedron Letters* **1987**, *28*, 3217.

Issued United States Patents:

1. U.S. patent 6,828,338, 2004 - Substituted polycyclic aryl and heteroaryl pyridines useful for selective inhibition of serine proteases of the coagulation cascade.

2. U.S. patent 6,750,342, 2004 - Substituted polycyclic aryl and heteroaryl pyrimidinones useful for selective inhibition of serine proteases of the coagulation cascade.

3. U.S. patent 6,693,121, 2004 - Polycyclic aryl and heteroaryl 4-pyridones useful for selective inhibition of serine proteases of the coagulation cascade.

4. U.S. patent 6,664,255, 2003 - Substituted polycyclic aryl and heteroaryl pyrazinones useful for selective inhibition of serine proteases of the coagulation cascade.

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7. U.S. patent 6,525,041, 2003 – Manganese or Iron complexes of nitrogen-containing macrocyclic ligands effective as catalysts for dismuting superoxide.

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10. U.S. Patent 6,084,093, 2000 - Manganese Complexes of Nitrogen-Containing Macrocyclic Ligands Effective as Catalysts for Dismutating Superoxide.

11. U.S. Patent 5,976,498, 1999 - Methods of Diagnostic Image Analysis Using Metal Complexes of Nitrogen-Containing Macrocyclic Ligands.

12. U.S. Patent 5,908,931, 1999 - Preorganized Hexadentate Ligands Useful in Radiographic Imaging agents.

13. U.S. Patent 5,874,421, 1999 - Manganese Complexes of Nitrogen-Containing Macrocyclic Ligands Effective as Catalysts for Dismutating Superoxide.

14. U.S. Patent 5,637,578, 1997 - Manganese Complexes of Nitrogen-Containing Macrocyclic Ligands Effective as Catalysts for Dismutating Superoxide.
15. U.S. Patent 5,648,060, 1997 - Preorganized Hexadentate Ligands Useful in Radiographic Imaging agents.

16. U.S. Patent 5,610293, 1997 - Methods of Preparing Manganese Complexes of Nitrogen-Containing Macrocyclic Ligands.

17. U.S. Patent 5,248,498, 1993 - Fullerene Compositions For Magnetic Resonance Spectroscopy and Imaging.

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19. U.S. Patent 5,112,594, 1992 - Kit for Preparing a Technetium-99m Myocardial Imaging Agent.

20. U.S. Patent 5,112,595, 1992 - 99M-Tc(III) Myocardial Imaging Agents and Method of Use.

21. U.S. Patent 5,104,014, 1992 - Synthesis of Vicinal Diamines.

United States Patents Pending:

1. WO 2007149479 - Fluorescent pyrazine derivatives and methods of using the same in assessing renal function (Covidien).

2. WO 2007149478 - Preparation of pyrazine derivatives for optical detection in medical procedures.

3. WO 2006071759 – Fluorescent pyrazines and methods of using the same in assessing renal function (Mallinckrodt Imaging – Tycohealthcare).

4. WO 2006069326 – Polyethylene glycolated superioxide dismutase mimetics (Metaphore Pharmaceuticals).

5. U.S.. patent application 20040106626 - 6-Membered unsaturated heterocyclic compounds useful for selective inhibition of the coagulation cascade (prodrugs). (Pharmacia-Pfizer).

6. U.S. patent application 20040092812 - Methods and contrast agents useful for quantifying nitric oxide. (Pharmacia-Pfizer).

7. U.S. patent application 20040082585 - *Prodrugs* of substituted polycyclic compounds useful for selective inhibition of the coagulation cascade. (Pharmacia-Pfizer).

8. U.S. patent application 20040077625 - Preparation of novel 1,4-benzothiazepine and 1,5-benzothiazepine compounds as inhibitors of apical sodium co-dependent bile acid transport and taurocholate uptake. (Pharmacia-Pfizer).
9. U.S. patent application 20020183307 - Preparation of novel 1,4-benzothiazepine and 1,5-benzothiazepine compounds as inhibitors of apical sodium co-dependent bile acid transport and taurocholate uptake. (Pharmacia-Pfizer).

Selected Presentations:

1. "New Optical Probes For The Continuous Monitoring of Renal Function" presented at: Photonics West Biomedical Optics Symposium, January 19-24, 2008.

2. "Confessions of a St. Louis Sep-Funnel Shaker" American Chemical Society St. Louis Award Address, presented April 15, 2007.

3. "From Methanogenic Archaea to the Parallel Medicinal Chemistry Lab" presented at the Department of Biochemistry and Molecular Biology, Saint Louis University Medical School, Sept. 18, 2006 (Invited).

4. "Synthesis, Characterization, and Solution ^{113}Cd NMR Analysis of Cd(II) 1,4,7,10,13-Pentaazacyclopentadecane Complexes" presented at: The XXIII International Symposium on Macrocyclic Chemistry, Oahu Hawaii, June 7-12, 1998.

5. "The Pseudopeptide Synthesis of Functionalized Pentaazamacrocycles" presented at: The Second Winter Conference On Medicinal and Bioorganic Chemistry, Steamboat Springs, Colorado, January 26-31, 1997.

6. "Synthesis of Functionalized Polyazamacrocycles: Preorganizing Peptide Cyclization Modes." Presented at the XIX International Symposium on Macrocyclic Chemistry, June 12-17, 1994. The University of Kansas, Lawrence, Kansas.

7. "The Asymmetric Synthesis of Functionalized Polyazamacrocycles: Applications to Synthetic Metalloenzyme Mimics", 1993 Distinguished Alumni Lecture, University of Missouri - St. Louis, May 1993.

8. "Design and Synthesis of New Preorganized Hexachelating $N_2O_2P_2$ Ligand Systems for Metal-Based Radiopharmaceutical Applications." Presented at the 38th annual meeting of The Society of Nuclear Medicine, ST. Louis, MO, 1991.

9. "Synthesis of Tripodal Hexadentate Ligand Systems for Tc-99m Radiopharmaceutical Applications." Presented at the 37th annual meeting of The Society of Nuclear Medicine, Washingtion, D.C., 1990.